DEPARTMENT OF HEALTH & HUMAN SERVICES

PMS

Public Health Service

P910018

Memorandum

Date FEB 21 1996

From Director, Office of Device Evaluation (HFZ-400)
Center for Devices and Radiological Health (CDRH)

Subject Premarket Approval of Kaneka America Corporation
Liposorber® LA-15 System - Action

To The Director, CDRH
ORA _____

ISSUE. Publication of a notice announcing approval of the subject PMA.

FACTS. Tab A contains a FEDERAL REGISTER notice announcing:

(1) a premarket approval order for the above referenced medical device (Tab B); and

(2) the availability of a summary of safety and effectiveness data for the device (Tab C).

RECOMMENDATION. I recommend that the notice be signed and published.

Susan Alpert, Ph.D., M.D.

Attachments

Tab A - Notice
Tab B - Order
Tab C - S & E Summary

DECISION

Approved _____ Disapproved _____ Date _____

Prepared by: Linda Dart, CDRH, HFZ-470, August 21, 1995, 594-1220
Cathy Nutter, CDRH, HFZ-470, August 21, 1995, 594-1212
Elias Mallis, CDRH, HFZ-470, August 21, 1995, 594-1220
Miriam Provost, Ph.D., CDRH, HFZ-470, August 21, 1995, 594-1220

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DRAFT

DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

[DOCKET NO. _____]

APPLICANT: Kaneka America Corporation

PREMARKET APPROVAL OF: Liposorber® LA-15 System

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) is announcing its approval of the application by Kaneka America Corporation, New York, NY, for premarket approval, under section 515 of the Federal Food, Drug, and Cosmetic Act (the act), of the Liposorber® LA-15 System. After reviewing the recommendation of the Gastroenterology and Urology Devices Panel, FDA's Center for Devices and Radiological Health (CDRH) notified the applicant, by letter on FEB 21 1996, of the approval of the application.

DATE: Petitions for administrative review by (insert date 30 days after date of publication in the FEDERAL REGISTER).

ADDRESS: Written requests for copies of the summary of safety and effectiveness data and petitions for administrative review, to the Dockets Management Branch (HFA-305), Food and Drug Administration, Rm. 1-23, 12420 Parklawn Drive, Rockville, MD 20857.

FOR FURTHER INFORMATION CONTACT:

Linda Dart

Center for Devices and Radiological Health (HFZ-470)

Food and Drug Administration

9200 Corporate Blvd.

Rockville, MD 20850

301-594-1220.

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SUPPLEMENTARY INFORMATION: On October 3, 1991, Kaneka America Corporation, New York, NY 10022, submitted to CDRH an application for premarket approval of the Liposorber® LA-15 System. The device is a low density lipoprotein (LDL) apheresis system, indicated for use in performing low density lipoprotein cholesterol (LDL-C) apheresis to acutely remove LDL-C from the plasma of the following high risk patient populations for whom diet has been ineffective and maximum drug therapy has either been ineffective or not tolerated: Group A - functional hypercholesterolemic homozygotes with LDL-C > 500 mg/dl; Group B - functional hypercholesterolemic heterozygotes with LDL-C ≥ 300 mg/dl; and Group C - functional hypercholesterolemic heterozygotes with LDL-C ≥ 200 mg/dl and documented coronary heart disease.

The LDL-C levels for the indicated patient populations are baseline LDL-C levels obtained after the patient has had, at a minimum, a 6 month trial of an American Heart Association (AHA) Step II diet (or equivalent) and maximum tolerated combination drug therapy designed to reduce LDL-C. Maximum tolerated combination drug therapy is an adequate trial of drugs from at least two separate classes of hypolipidemic agents such as, bile acid sequesterants, HMG-CoA reductase inhibitors, fibric acid derivatives, Niacin/Nicotinic Acid, etc. Documented coronary heart disease (CHD) includes documentation of coronary artery disease by coronary angiography or a history of myocardial infarction (MI), coronary artery bypass surgery (CABG), percutaneous transluminal coronary angioplasty (PTCA) or alternative revascularization procedure (e.g. atherectomy or stent), or progressive angina documented by exercise or non-exercise stress test. Baseline lipid levels are to be determined after stabilization on diet and drug therapy by making two measurements during a 2 to 4 week period. (Note: the two values should be within 10% of each other, indicating a stable condition.)

Although clinical benefit of LDL-C lowering has been documented in several diet, drug and/or surgical intervention trials, clinical studies using the LIPOSORBER® LA-15 system were not designed to address and did not establish the long-term clinical benefit of acutely lowering LDL-C.

On April 21, 1995, the Gastroenterology and Urology Devices Panel, an FDA advisory panel, reviewed and recommended approval of the application.

On FEB 21 1996, CDRH approved the application by a letter to the applicant from the Director of the Office of Device Evaluation, CDRH.

A summary of the safety and effectiveness data on which CDRH based its approval is on file in the Dockets Management Branch (address above) and is available from that office upon written request. Requests should be identified with the name of the device and the docket number found in brackets in the heading of this document.

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OPPORTUNITY FOR ADMINISTRATIVE REVIEW

Section 515(d)(3) of the act (21 U.S.C. 360e(d)(3)) authorizes any interested person to petition, under section 515(g) of the act (21 U.S.C. 360e(g)), for administrative review of CDRH's decision to approve this application. A petitioner may request either a formal hearing under part 12 (21 CFR part 12) of FDA's administrative practices and procedures regulations or a review of the application and CDRH's action by an independent advisory committee of experts. A petition is to be in the form of a petition for reconsideration under 10.33(b) (21 CFR 10.33(b)). A petitioner shall identify the form of review requested (hearing or independent advisory committee) and shall submit with the petition supporting data and information showing that there is a genuine and substantial issue of material fact for resolution through administrative review. After reviewing the petition, FDA will decide whether to grant or deny the petition and will publish a notice of its decision in the FEDERAL REGISTER. If FDA grants the petition, the notice will state the issue to be reviewed, the form of the review to be used, the persons who may participate in the review, the time and place where the review will occur, and other details.

Petitioners may, at any time on or before (insert date 30 days after date of publication in the FEDERAL REGISTER), file with the Dockets Management Branch (address above) two copies of each petition and supporting data and information, identified with the name of the device and the docket number found in brackets in the heading of this document. Received petitions may be seen in the office above between 9 a.m. and 4 p.m., Monday through Friday.

This notice is issued under the Federal Food, Drug, and Cosmetic Act

(secs. 515(d), 520(h), (21 U.S.C. 360e(d), 360j(h)) and under authority delegated to the Commissioner of Food and Drugs (21 CFR 5.10) and redelegated to the Director, Center for Devices and Radiological Health (21 CFR 5.53).

Dated:_____.

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
9200 Corporate Boulevard
Rockville MD 20856

Mr. William J. Wood
Director of Marketing and
Development Medical Devices
Kaneka America Corporation
65 East 55th Street
New York, New York 10022

FEB 21 1996

Re: P910018
Liposorber® LA-15 System
Filed: October 3, 1991
Amended: October 3, December 20 and 27, 1991; January 30, March 3, 12, October 1, and November 13, 1992; April 26, June 25, October 8, and December 20, 1993; June 15, November 22, and December 6, 1994; March 14, 15, 25, June 9, July 6, September 19, 28, October 2, 4, 6, 20, and December 15, 1995; and January 30, 1996

Dear Mr. Wood:

The Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration (FDA) has completed its review of your premarket approval application (PMA) for the Liposorber® LA-15 System. The device is a low density lipoprotein (LDL) apheresis system, indicated for use in performing low density lipoprotein cholesterol (LDL-C) apheresis to acutely remove LDL-C from the plasma of the following high risk patient populations for whom diet has been ineffective and maximum drug therapy has either been ineffective or not tolerated: Group A - functional hypercholesterolemic homozygotes with LDL-C > 500 mg/dl; Group B - functional hypercholesterolemic heterozygotes with LDL-C ≥ 300 mg/dl; and Group C - functional hypercholesterolemic heterozygotes with LDL-C ≥ 200 mg/dl and documented coronary heart disease.

The LDL-C levels for the indicated patient populations are baseline LDL-C levels obtained after the patient has had, at a minimum, a 6 month trial of an American Heart Association (AHA) Step II diet (or equivalent) and maximum tolerated combination drug therapy designed to reduce LDL-C. Maximum tolerated combination drug therapy is an adequate trial of drugs from at least two separate classes of hypolipidemic agents such as, bile acid sequesterants, HMG-CoA reductase inhibitors, fibric acid derivatives, Niacin/Nicotinic Acid, etc. Documented coronary heart disease (CHD) includes documentation of coronary artery disease by coronary angiography or a history of myocardial infarction (MI), coronary artery bypass surgery (CABG), percutaneous transluminal coronary angioplasty (PTCA) or alternative revascularization procedure (e.g. atherectomy or stent), or progressive angina documented by exercise or non-exercise stress test. Baseline lipid levels are to be determined after stabilization on diet and drug therapy by making two measurements during a 2 to 4 week period. (Note: the two values should be within 10% of each other, indicating a stable condition.)

Although clinical benefit of LDL-C lowering has been documented in several diet, drug and/or surgical intervention trials, clinical studies using the LIPOSORBER® LA-15 system were not designed to address and did not establish the long-term clinical benefit of acutely lowering LDL-C.

We are pleased to inform you that the PMA is approved subject to the conditions described below and in the "Conditions of Approval" (enclosed). You may begin commercial distribution of the device upon receipt of this letter.

The sale, distribution, and use of this device are restricted to prescription use in accordance with 21 CFR 801.109 within the meaning of section 520(e) of the Federal Food, Drug, and Cosmetic Act (the act) under the authority of section 515(d)(1)(B)(ii) of the act. FDA has also determined that to ensure the safe and effective use of the device that the device is further restricted within the meaning of section 520(e) under the authority of section 515(d)(1)(B)(ii), (1) insofar as the labeling specify the requirements that apply to the training of practitioners who may use the device as approved in this order and (2) insofar as the sale, distribution, and use must not violate sections 502(q) and (r) of the act.

In addition to the postapproval requirements in the enclosure, this approval is subject to an open-ended patient registry/post-approval study for all patients using the device. Patient data is to be collected and a report generated and submitted annually to FDA for review. This report will include a summary of adverse events, morbidity and mortality statistics, analysis of lipid and chemistry laboratory results and summary statistics on demographics and other baseline characteristics of registry patients. In addition to the annual report, all patient deaths are to be reported to the FDA within 10 days after the applicant receives or has knowledge of information concerning the death. The mortality statistics are to be submitted on a quarterly basis and will include all patient information for patients who have died, whether the death is related or unrelated to the device. The timely reporting of such events is necessary owing to the limited device experience. The quarterly reports will continue until FDA determines the reporting frequency is no longer needed.

Expiration dating for this device has been established and approved at 4 years for the Sulflux® FS-05 Plasma Separator and the Liposorber® LA-15 LDL Adsorption Column, and at 3 years for the Tubing System for Plasmapheresis (LT-MA2).

CDRH will publish a notice of its decision to approve your PMA in the FEDERAL REGISTER. The notice will state that a summary of the safety and effectiveness data upon which the approval is based is available to the public upon request. Within 30 days of publication of the notice of approval in the FEDERAL REGISTER, any interested person may seek review of this decision by requesting an opportunity for administrative review, either through a hearing or review by an independent advisory committee, under section 515(g) of the Federal Food, Drug, and Cosmetic Act (the act).

Failure to comply with the conditions of approval invalidates this approval order. Commercial distribution of a device that is not in compliance with these conditions is a violation of the act.

You are reminded that as soon as possible, and before commercial distribution of your device, that you must submit an amendment to this PMA submission with copies of all approved labeling in final printed form.

All required documents should be submitted in triplicate, unless otherwise specified, to the address below and should reference the above PMA number to facilitate processing.

PMA Document Mail Center (HFZ-401)
Center for Devices and Radiological Health
Food and Drug Administration
9200 Corporate Blvd.
Rockville, Maryland 20850

If you have any questions concerning this approval order, please contact Ms. Linda Dart at (301) 594-1220.

Sincerely yours,

Susan Alpert, Ph.D., M.D.
Director
Office of Device Evaluation
Center for Devices and
Radiological Health

Enclosure

SUMMARY OF SAFETY AND EFFECTIVENESS DATA
LIPOSORBER® LA-15 System

I. GENERAL INFORMATION

DEVICE GENERIC NAME: LDL Apheresis System

DEVICE TRADE NAME: LIPOSORBER® LA-15 System

APPLICANT'S NAME AND ADDRESS: Kaneka America Corporation
65 East 55th Street, 12th Floor
New York, New York 10022

PREMARKET APPROVAL APPLICATION (PMA) NUMBER: P910018

DATE OF PANEL RECOMMENDATION: April 21, 1995

DATE OF NOTICE OF APPROVAL TO THE APPLICANT: FEB 27 1996

II. INDICATIONS FOR USE

The LIPOSORBER® LA-15 System is indicated for use in performing low density lipoprotein cholesterol (LDL-C) apheresis to acutely remove LDL-C from the plasma of the following high risk patient populations for whom diet has been ineffective and maximum drug therapy has either been ineffective or not tolerated:

Group A. Functional Hypercholesterolemic Homozygotes with LDL-C > 500 mg/dl;

Group B. Functional Hypercholesterolemic Heterozygotes with LDL-C ≥ 300 mg/dl; and

Group C. Functional Hypercholesterolemic Heterozygotes with LDL-C ≥ 200 mg/dl and documented coronary heart disease.

The LDL-C levels for the indicated patient populations are baseline LDL-C levels obtained after the patient has had, at a minimum, a 6 month trial of an American Heart Association (AHA) Step II diet (or equivalent) and maximum tolerated combination drug therapy designed to reduce LDL-C. Maximum tolerated combination drug therapy is an adequate trial of drugs from at least two separate classes of hypolipidemic agents such as, bile acid sequesterants, HMG-CoA reductase inhibitors, fibric acid derivatives, Niacin/Nicotinic Acid, etc. Documented coronary heart disease (CHD) includes documentation of coronary artery

disease by coronary angiography or a history of myocardial infarction (MI), coronary artery bypass surgery (CABG), percutaneous transluminal coronary angioplasty (PTCA) or alternative revascularization procedure (e.g. atherectomy or stent), or progressive angina documented by exercise or non-exercise stress test. Baseline lipid levels are to be determined after stabilization on diet and drug therapy by making two measurements during a 2 to 4 week period. (Note: the two values should be within 10% of each other, indicating a stable condition.)

Although clinical benefit of LDL-C lowering has been documented in several diet, drug and/or surgical intervention trials, clinical studies using the LIPOSORBER® LA-15 system were not designed to address and did not establish the long-term clinical benefit of acutely lowering LDL-C.

III. DEVICE DESCRIPTION

COMPONENTS

The device is an integrated extracorporeal blood processing system that includes the following 3 single use/disposable components and a control/monitor unit:

1. The SULFLUX® FS-05 Plasma Separator (disposable) is comprised of approximately 2800 polysulfone hollow fibers encased in a polycarbonate housing, used to separate plasma from a patient's whole blood.

2. The LIPOSORBER® LA-15 LDL Adsorption Column (disposable) is comprised of two columns and a membrane filter unit. Each column contains a microporous (i.e., 64-160 μm particles) hydrophilic gel composed of 150 ml dextran sulfate cellulose (DSC) soaked in 0.04-0.08 w/v % sodium citrate/citric acid solution.

3. The Tubing System for Plasmapheresis (LT-MA2) (disposable) is a polyvinyl chloride tubing set specifically designed for the LIPOSORBER® LA-15 System.

4. The Apheresis Unit MA-01 is a microprocessor-controlled unit that monitors and regulates the LDL-apheresis procedure. It does this by controlling the various system pumps (e.g., heparin, blood, plasma, and regeneration) and valves, by responding to sensors and alarms, and by storing key operational parameters for system calculations throughout the procedure.

PRINCIPLE OF OPERATION

Blood is withdrawn from the patient via a simple blood access (e.g., large vein venipuncture). The blood is combined with heparin and is continually pumped at a steady flow rate ranging from 80-100 ml/min through the LT-MA2 tubing system into the blood inlet port of the SULFLUX® FS-05 Plasma Separator. The separator contains a semi-permeable hollow fiber membrane which allows plasma to pass across the fibers while the

larger, cellular elements are excluded. The cellular elements exit through the blood exit port and are later returned to the patient with no further processing while the plasma exits the separator through the plasma exit port and is then pumped to one of the two LIPOSORBER® LA-15 LDL Adsorption Columns. The DSC in the column has a strong affinity for apolipoprotein B (ApoB) containing lipoproteins (e.g., LDL, very low density lipoprotein cholesterol (VLDL-C) and Lipoprotein (a) (Lp(a)) and adsorbs these elements from the plasma. After passing through the DSC column and a filter membrane, which ensures that no particles from the column enter the system, the plasma is recombined with the cellular elements and returned to the patient. The extracorporeal volume of the system, at any one time, is 400 ml (230 ml plasma and 170 ml of blood cell components). The entire procedure, which is controlled by the MA-01 Apheresis Unit, takes between 3 and 4 hours to treat 1 to 1.5 plasma volumes.

For the initial treatment phase, a total of 500 ml of plasma is processed by one column, whereas for all subsequent phases, a total of 600 ml of plasma is processed before regeneration is required. Because the amount of plasma that may be treated with one column is limited, the Apheresis Unit activates the regeneration process of the saturated column while the other column is in use. To regenerate a column, a hypertonic saline solution is flushed through the column causing the lipoproteins to desorb from the DSC sorbent. The resulting fluid is drained from the column and released to a waste chamber. Finally, the column is rinsed with Ringer's solution so that it is ready for the next treatment phase.

IV. CONTRAINDICATIONS

LDL-apheresis with the LIPOSORBER® LA-15 System is contraindicated in patients:

1. for whom the use of heparin would cause excessive or uncontrolled anticoagulation or for whom adequate anticoagulation cannot be safely achieved, such as patients with hemophilia or patients who have had recent surgery; or

2. with known hypersensitivity to heparin or ethylene oxide.

The warnings and precautions can be found in the LIPOSORBER® LA-15 System labeling (Attachment 1).

V. ALTERNATIVE PRACTICES OR PROCEDURES

Cholesterol lowering drugs and maximal diet therapy may not adequately reduce the cholesterol levels of patients with familial hypercholesterolemia (FH). All homozygous FH patients and severe heterozygous FH patients are usually included in this category. In order to treat these patients, various nonpharmacological alternatives may be attempted, including partial ileal bypass, portacaval shunt surgery, liver transplantation and plasmapheresis.

VI. MARKETING HISTORY

The LIPOSORBER® LA-15 System has been commercially distributed in the following countries since the date indicated in parentheses: Japan (December 1987), the Netherlands (December 1987), Italy (January 1988), France (December 1989), Belgium (July 1990), and Germany (January 1995). The LIPOSORBER® LA-15 System has not been withdrawn from marketing in any jurisdiction for any reason relating to safety and effectiveness of the device.

VII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE

Potential adverse reactions associated with LDL-apheresis using this system are those expected in any procedure involving extracorporeal circulation. Reactions, listed by frequency of occurrence, included hypotension, nausea/vomiting, flushing/blotching, angina/chest pain, fainting, lightheadedness, anemia, abdominal discomfort, numbness/tingling, tachycardia, headache, shortness of breath, hemolysis, bradycardia, itching/hives, arrhythmia, vasovagal reaction, prolonged bleeding, chills, diaphoresis, and blood loss.

Patients on certain antihypertensive drugs, such as diuretics, calcium antagonists, beta blockers and angiotensin converting enzyme (ACE) inhibitors, may have an increased risk of hypotensive reactions during extracorporeal therapy. In particular, ACE inhibitors, when used in conjunction with LDL-apheresis, can cause severe hypotension associated with flushing, dyspnea, and bradycardia. In order to minimize the risks associated with concomitant hypertensive medication it is recommended that patients refrain from taking antihypertensive drugs at least 24 hours prior to the LDL-apheresis procedure. If the administration of antihypertensive medications cannot be interrupted, the treating physician should consider a decreased dosage for the days of therapy.

Vascular access related problems such as hematoma formation at the site of venipuncture, air embolism, excessive bleeding from the anticoagulant, and blood clotting may occur. In addition, there is the potential for infectious disease transmission (including hepatitis) and sepsis due to circuit contamination. Other complications such as significant blood or plasma loss from extracorporeal circuit leaks; fluid imbalance; hypersensitivity reactions; and coagulopathy, potentially extending several days post-treatment, may also occur. Anemia may result from the repetitive extracorporeal procedures and/or from periodic blood sampling.

Equipment malfunction or user error may result in patient fluid volume abnormalities which may require acute medical intervention. In addition, because a substantial surface area of tubing is exposed to ambient temperature, the cooling of priming solution or blood may be sufficient to induce chills. The LIPOSORBER® LA-15 System is equipped with a thermal blood warmer connected to the blood return (venous) line to warm the blood prior to its return to minimize this effect.

LDL-apheresis is known to acutely decrease the following serum components: hemoglobin, vitamin E, albumin, fibrinogen and platelets. The long term effects of this are not known.

Although the procedure does not pose a significant risk of angina, myocardial infarctions or other adverse cardiovascular events, the possibility of such reactions cannot be totally excluded. In addition, the possibility of death resulting from treatments with the device cannot be totally excluded.

See the Section IX, Summary of Clinical Studies, for additional information.

VIII. SUMMARY OF PRECLINICAL STUDIES

BIOCOMPATIBILITY TESTING

The LIPOSORBER® LA-15 System includes the following three disposable device components: SULFLUX® FS-05 Plasma Separator, LIPOSORBER® LA-15 LDL Adsorption Column, and Blood Tubing System for Plasmapheresis (LT-MA2). Biocompatibility tests were conducted on the patient-contacting materials in the device and included: cytotoxicity, hemolysis, muscle implantation (3 day), animal and *in vitro* toxicological studies, immunological, sterility and pyrogenicity studies. The results showed the materials in the device to be safe for the intended use.

BENCH TESTING

The applicant conducted testing that evaluated the physicochemical properties of the materials used in the device. The following tests were conducted: column stability, mesh filter and column deterioration, hollow fiber deterioration, and package deterioration.

The stability test evaluated the effect of sterilization on the adsorption capacity of the DSC. In this test, the adsorbent was sterilized and equilibrated with Ringer's solution, mixed with human plasma, and placed in a test tube in a 37°C water bath. The contents of the test tube were stirred every 5-20 minutes, with samples taken after 0.5, 1, and 2 hours, and the amounts of adsorbed total cholesterol (TC) and high density lipoprotein cholesterol (HDL-C) were measured. The test showed that sterilization had minimal effect on the adsorption capacity of the DSC.

The mesh filter and column deterioration tests evaluated the change in (1) the tensile strength of the mesh filter and (2) the bending strength of the adsorption column bodies. A total of 3 samples were tested, 1 sample prior to sterilization, 1 sample from 1-3 months after sterilization, and 1 sample a year after sterilization. The results showed that sterilization and storage had minimal effect on the tensile and bending strength of the device.

The material deterioration test evaluated the effect of the gamma irradiation on the tensile and elongation strength of the hollow fibers of the plasma separator. A total of 10 samples were tested prior to sterilization with gamma irradiation, and a total of 20 samples were tested after sterilization with gamma irradiation, 10 with 2.5 MRad and 10 with 5.0 MRad, at each of the following sterilization phases: immediately after, 3 months after, and 7 months after sterilization. The results of the testing showed that the hollow fibers retained their material properties after exposure to radiation and storage.

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The following package deterioration tests evaluated the effect of gamma irradiation on the quality of the packaging materials: tensile strength and percent elongation (in both transverse and longitudinal directions), strength to pinhole, percent transparency, percent haze, and strength of heat-sealed parts. A total of 10 samples (5 prior to sterilization with gamma radiation and 5 after sterilization with gamma irradiation (2.5 MRad)) were used for each deterioration test. The results showed that irradiation had minimal effect on the integrity of the packaging materials.

SHELF-LIFE TESTING

The applicant conducted testing that established the minimum shelf-life for the components of the device. The following tests for the SULFLUX® FS-05 Plasma Separator were conducted: pressure/leakage, extraction (appearance, foam extinction, UV absorption, and potassium permanganate ($KMnO_4$) reduction), membrane sealant, sterility, and biological (acute toxicity, pyrogenicity, intracutaneous reactivity, and hemolysis).

The following tests for the LIPOSORBER® LA-15 Adsorption Column were conducted: pressure/leakage, extraction (appearance, foam extinction, pH, zinc, UV absorption, $KMnO_4$ reduction, nonvolatile residue, and heavy metals), sterility, biological (acute toxicity, pyrogenicity, intracutaneous reactivity, and hemolysis), and microparticle leakage.

The following tests for the tubing system were conducted: material strength (durability, elasticity), extraction (appearance, foam extinction, pH, zinc, tin, $KMnO_4$ reduction, UV absorption, nonvolatile residue, and heavy metals), sterility, biological (acute toxicity, pyrogenicity, intracutaneous reactivity, and hemolysis), and implantation.

The above tests established a shelf-life of 4 years for the SULFLUX® FS-05 Plasma Separator, 4 years for the LIPOSORBER® LA-15 Adsorption Column, and 3 years for the Tubing System for Plasmapheresis (LT-MA2).

SOFTWARE TESTING

Testing of the software included both functional and integration tests conducted throughout the entire development of the software. This includes the validation and verification testing and hazard analysis conducted on the finished device.

Emulation of the software evaluated the accuracy of (1) the transitions between operational modes, (2) the operations in the maintenance modes, and (3) the normal process modes, displays, sequence controls and alarms. Modular level testing of the software evaluated whether each module performed as designed. Bench testing of the device with water and bovine blood, which simulated actual patient treatment, was done under normal system operational conditions and sequences and under conditions that tested alarms for data inputs out of allowable ranges.

The results of the software testing showed that the software did perform according to specifications and that the design was appropriate for its intended use.

ELECTRICAL SAFETY TESTING

The LIPOSORBER® LA-15 System was tested in accordance with IEC 601 "Medical Electrical Equipment," IEC 62D (CO) 34 "Medical Electrical Equipment: Particular Requirements for Safety of Hemodialysis Equipment," and UL 544 "Medical and Dental Equipment." In particular, the device was tested for insulation resistance, insulation strength, and current leakage.

The results of the tests showed that the device met the safety requirements of the above standards.

IX. SUMMARY OF CLINICAL STUDY

OBJECTIVE

The overall objective of this study was to evaluate the safety and effectiveness of the LIPOSORBER® LA-15 System in performing LDL-apheresis to lower LDL-C and TC levels in high risk patient populations for whom diet has been ineffective and maximum drug therapy has either been ineffective or not tolerated.

STUDY DESIGN

The original clinical trial of the LIPOSORBER® LA-15 System was conducted as a multicenter study under investigation device exemption (IDE) G880069 at 9 sites in the United States from December 1988 to September 1991.

Patients of both sexes from ages 5 to 70 years meeting the following inclusion/exclusion criteria were eligible for the clinical investigation:

Inclusion criteria

- FH homozygote
- FH heterozygote with TC greater than 240 mg/dl
  - despite stabilization on appropriate diet and maximal combination drug therapy; or
  - on an appropriate diet and with a documented history of drug intolerance.
- Non-FH patients with TC greater than 240 mg/dl
  - despite stabilization on appropriate diet and maximal combination drug therapy; or
  - on an appropriate diet and with a documented history of drug intolerance.

Exclusion criteria

- Pregnant women;
- Below 5 years of age or over 70 years of age;
- Body weight less than 15 kgs or greater than 30% above ideal;
- Severe cardiac disorders such as malignant arrhythmias or decompensated congestive heart failure (New York Heart Association Class 4);
- MI or cerebral vascular accident within the previous 4 months;
- Coagulation abnormalities or intolerance to the extracorporeal system;
- Severe, uncontrollable hyper- or hypotension;
- Severe liver function abnormalities; or
- Severe metabolic disorders or any other medical condition that, in the judgement of the investigator, may interfere with safe apheresis treatment.

Based on FDA guidance, which resulted from expert opinions on issues of clinical endpoints and target patient population groups, the patients who received treatments in clinical trials of LDL-apheresis devices were classified into the following groups:

Functional homozygotes

Group A: LDL-C > 500 mg/dl

Functional heterozygotes

Group B: LDL-C ≥ 300-499 mg/dl

Group C: LDL-C ≥ 200 mg/dl and CHD, manifested by history of MI, CABG, angioplasty or angina.

Based upon these classifications, the clinical trial enrolled:

5 homozygotes (Group A)

10 heterozygotes (Group B)

24 heterozygotes with CHD (Group C)

An additional 25 patients were treated who did not fit into one of the categories given above. Although detailed effectiveness data was reported and statistically analyzed from 2,229 LDL-apheresis procedures performed from December 14, 1988 through September

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30, 1991, for all 64 patients, only data from the 39 patients within the indicated patient Groups A, B, and C are included in the analysis of the effectiveness of the device. Safety analysis of the device includes data from all patients enrolled in the study. The study did not include a control group. Twenty nine of the 64 patients were treated for a minimum of 11 months.

The majority of the heterozygote patients were over the age of 40. Two of the homozygotes were 20 to 29 years old and 3 were children less than 14 years of age. The study group included 37 males and 27 females. Of these 64 patients, 56 were white, 5 were black and 3 were Hispanic.

TREATMENT PROTOCOL

The clinical trial included screening, study and optional follow-up periods. During the screening period, the patients received maximal drug and diet therapy and their baseline cholesterol levels were established. The study period was conducted in three parts: a 6 week period in which patients were to be treated once every 2 weeks followed by two 6 week periods in which treatment intervals were determined by the administering physician. Treatment intervals in the study period ranged from 4 to 63 days. Following 18 weeks of therapy, the treatments were stopped for 4 weeks to observe the kinetics of the return of the patient's LDL-C and TC levels to baseline. Following the study period, the patients were offered the option of discontinuing treatments or entering the follow-up period and continue receiving LDL-apheresis with the treatment interval determined by their physician according to his/her clinical judgement. In the Clinical Trial, treatment intervals of the follow-up period varied from 7 to 143 days.

Each apheresis procedure was targeted to achieve a post-treatment TC level of approximately 100 mg/dl. The volume of plasma that was treated was adjusted according to the patient's body weight, height, sex, hematocrit and pre-treatment level of LDL-C, according to a formula developed by Kaneka America Corporation.

CLINICAL ENDPOINTS

The acute lowering (reduction immediately following treatment) of plasma LDL-C and TC were the criteria used to assess the effectiveness of the LIPOSORBER® LA-15 system in the target patient population.

CLINICAL RESULTS

1. Acute Lipid Lowering Effect of LIPOSORBER® LA-15 System

   The average percent lowering of LDL-C, TC and HDL-C after treatment during the study period of the clinical trial is shown in Table 1. In compiling these results, the average reduction for each treatment group was computed using at least 50 treatment values.

Table 1

Percent lowering after treatment of LDL-C, TC, and HDL-C (averaged for all treatments during "study period" of clinical trial)

Patient Classification	LDL-C	TC	HDL-C
homozygotes (Group A) N = 5	76.7 - 84.5%	69.8 - 73.4%	11.1 - 15.4%
heterozygotes (Group B) N = 10	72.1 - 79.7%	62.4 - 64.3%	5.8 - 8.6%
heterozygotes (Group C) N = 22	74.5 - 79.2%	61.6 - 62.8%	2.2 - 6.2%

2. Rebound of LDL-C Levels

A patient's LDL-C levels begin to rebound (i.e., return to baseline levels) immediately after treatment at a nonlinear rate (more rapidly immediately post-treatment). LDL-C levels return to between 39 and 73 percent of baseline levels by day 7 and between 49 and 103 percent by day 14 as shown in Table 2:

Table 2

Range of rebound of LDL-C after treatment during study period

Number of Days After Treatment	Cumulative Mean Percentage Rebound to Baseline		
	Group A (N = 5*)	Group B (N = 10)	Group C (N = 22**)
1	9 - 19	8 - 18	6 - 16
2	14 - 26	15 - 25	20 - 32
3	23 - 39	25 - 35	24 - 56
5	31 - 51	38 - 52	42 - 58
7	39 - 57	43 - 73	47 - 73
14	49 - 91	69 - 99	65 - 103

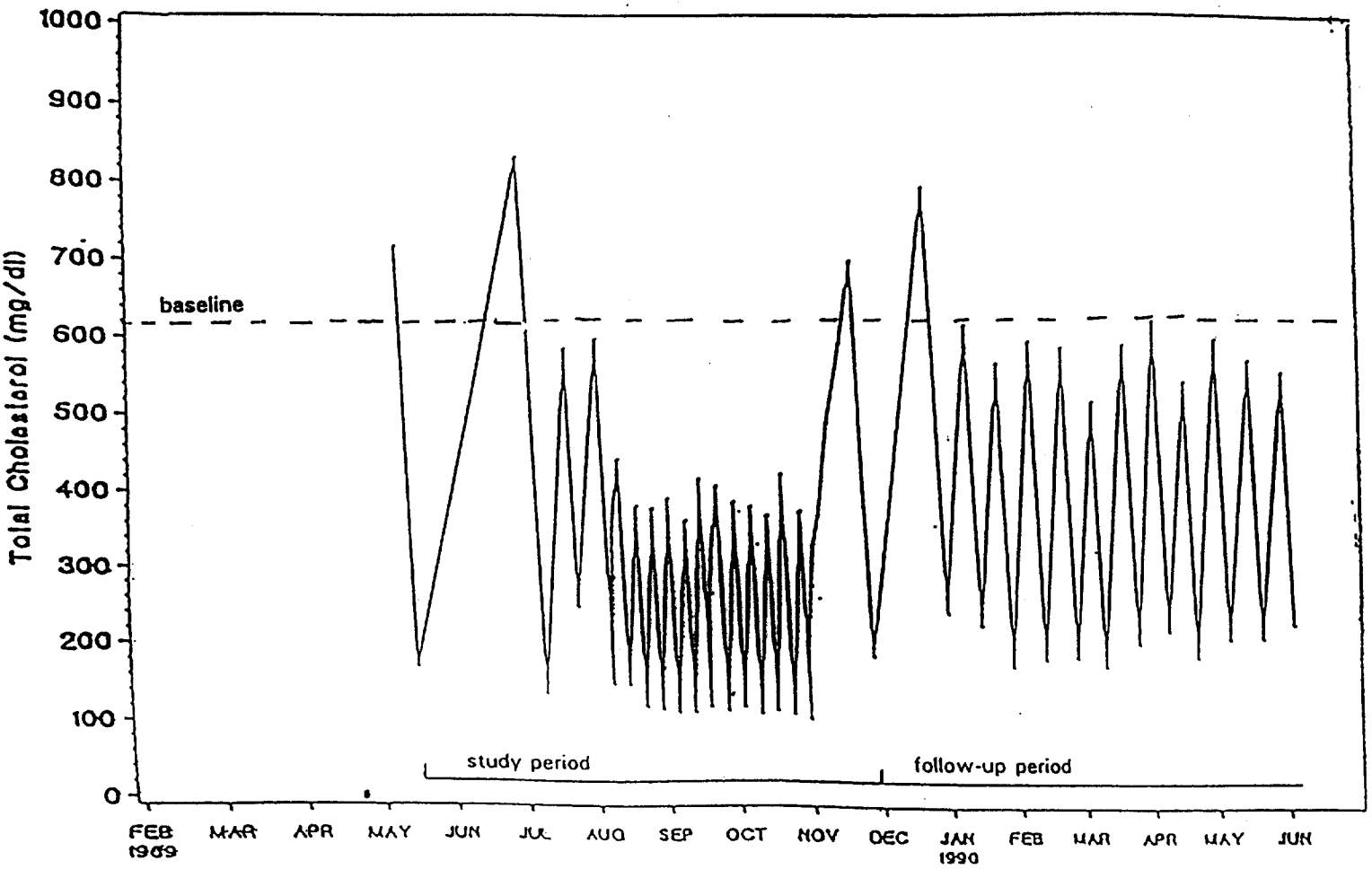
* N = number of patients

** Group C also included two patients who were not included in this analysis of study patients.

Without regular treatments, a patient's LDL-C and TC levels will rebound to baseline levels achieved with diet and drug therapy. The rate of rebound will accelerate if diet and lipid-lowering drug therapy are discontinued. With regular apheresis treatments, a patient's cholesterol levels can be maintained below the baseline. As shown in Figure 1, TC levels were maintained at a lower level when the patient received more frequent treatments, as in the study period, than those TC levels that were achieved when treatments were performed on a regular but less frequent schedule, as in the follow-up period.

Figure 1

TC levels in a patient from Group A receiving treatments with the LIPOSORBER® LA-15 System



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3. Effect of Treatment on other Plasma Components

The average change after treatment in the levels of other plasma components, such as apolipoprotein A1 (ApoA1) and Lp(a), are shown in Table 3. The reduction in these components varied by disease group. Patients classified as Group A, show statistically significant greater percent reduction in TC, HDL-C, non-HDL-C, LDL-C, ApoA1, ApoA2 and Lp(a) compared to the heterozygote Groups B and C. This is a result of the larger ratio of treated plasma volume to patient plasma volume. The ratios of treated plasma volume to patient plasma volume were 1.54 in Group A, 1.50 in Group B, and 1.37 in Group C. The differences in these ratios resulted from treating a larger volume of plasma and/or the small patient plasma volumes. For example, several of the patients in Group A were children and younger adults who had smaller plasma volumes.

Table 3

Acute reduction in other lipid components of plasma after treatment for all patients (Groups A, B and C) during the study period

Lipid Parameter	Group A N = 5 Mean %	std	Group B N = 10 Mean %	std	Group C N = 22 Mean %	std	Combined A, B & C N = 37 Mean %	std
Total Cholesterol	71.6	4.2	63.3	2.0	62.2	1.3	66.1	5.2
HDL-C	13.3	5.0	7.2	2.9	4.2	4.4	8.5	5.7
non HDL-C	79.0	5.8	74.6	2.9	74.9	3.2	76.4	4.7
LDL-C *	80.6	5.8	75.8	3.1	76.8	2.7	78.0	4.7
BQ-LDL-C†	78.1	6.6	74.8	6.4	73.6	4.7	75.3	6.0
VLDL-C	73.5	13.6	69.0	21.1	77.6	10.6	73.8	15.2
Triglycerides	56.1	11.7	55.7	4.8	61.1	12.5	57.6	10.6
ApoA1	19.5	5.8	16.6	6.8	13.3	4.3	15.9	6.0
ApoA2	24.5	12.5	12.7	11.0	13.4	12.8	16.2	12.9
ApoB	72.8	6.2	67.4	7.3	67.4	3.5	68.9	6.0
ApoE	53.8	41.7	51.8	12.2	62.4	12.1	56.9	23.7
Lp(a)	65.3	15.9	67.7	8.2	62.0	11.0	64.6	11.8

* Estimated from the Friedewald Equation
† Beta quantification/directly measured LDL-C

In addition, LDL-apheresis is known to acutely decrease the selected serum components listed in Table 4. The long-term effects of the reduction of these components have not been established.

Table 4

Mean percent reduction in selected serum components

Serum Components	Acute Percent Reduction (%)
Hemoglobin*	1.4
Vitamin E (α-tocopherol)**	63
Vitamin E (γ-tocopherol)**	55
Albumin*	14
Fibrinogen*	29
Platelet Counts*	17

* Data for the acute reductions in these serum components were obtained from 111 treatments (i.e., the first 3 treatments in 37 patients).

** Data for the acute reduction in Vitamin E were obtained from 185 treatments involving 15 patients.

4. Effect of Treatment on Blood Chemistry Profiles

Blood chemistries of all patients before and after treatment were analyzed across the first three treatments and are shown in Table 5. The only statistically significant changes that occurred between the baseline and study period were in fibrinogen, potassium, albumin and total protein levels; however, the observed means for these components were all within the normal ranges.

Table 5

Mean percent change in blood components after 1, 2 and 3 treatments for all patients (Groups A, B and C) during the study period

Blood component	Treatment 1 (%)	N	Treatment 2 (%)	N	Treatment 3 (%)	N	Total (%)	N
Red Blood Cells	- 3.4	29	- 2.3	29	- 2.9	27	- 1.4	215
White Blood Cells	+ 8.6*	29	+ 6.6*	29	+ 11.8*	27	+ 5.3	215
Platelet Count	- 9.6	29	- 16.9	29	- 14.6	27	- 16.9	214
Hemoglobin	- 3.4	29	- 2.6	29	- 2.9	27	- 1.4	215
Hematocrit	- 3.5	29	- 2.3	29	- 2.8	27	- 1.4	215
Fibrinogen	- 26.3	4	- 33.7	5	- 27.0	6	- 29.2	114
Total Protein	- 14.0	32	- 14.2	33	- 14.6	29	- 14.4	119
Albumin	- 14.0	32	- 13.4	33	- 13.5	29	- 13.8	117
Globulin	- 13.6	32	- 14.7	33	- 16.2	29	- 14.9	117
Total Bilirubin	+ 31.9	32	+ 31.0	33	+ 35.9	27	+ 31.9	117
SGOT (AST)	- 6.0	32	- 8.3	33	- 10.3	27	- 8.3	117
SGPT (ALT)	- 12.4	32	- 10.4	33	- 12.3	27	- 10.7	117
Alkaline Phosphatase	- 14.2	31	- 13.5	33	- 13.2	29	- 13.8	117
Total CPK	- 16.0	32	- 16.4	33	- 21.3	29	- 18.3	119
BUN	- 1.0*	32	- 0.1*	33	+ 0.8*	29	- 0.3*	117
Creatinine	- 2.5	32	- 4.7	33	- 2.6*	29	- 4.0	119
Uric Acid	- 1.5*	32	- 1.1*	33	- 1.6*	28	- 1.5*	118
Glucose	+ 16.1	32	+ 8.7*	33	+ 8.8*	28	+ 11.1	117
Sodium	+ 0.6	32	+ 1.0	33	+ 0.3*	27	+ 0.6	116
Potassium	- 6.2	31	- 8.7	32	- 4.9	27	- 6.5	114
Chloride	+ 2.3	32	+ 2.5	33	+ 2.6	27	+ 2.5	117
Inorganic Phosphorus	+ 0.8*	31	- 1.0*	33	+ 6.8	28	+ 1.3*	109
Calcium	- 6.7	30	- 6.3	33	- 7.2	29	- 6.9	109
IgG	- 15.1	29	-	0	- 8.9*	6	- 15.8	299
IgA	- 10.3	28	-	0	- 11.1*	6	- 14.0	299
IgM	- 23.7	30	-	0	- 18.9	6	- 19.8	301

* These mean percent changes are not significantly different from zero by t-test.

Hematology, coagulation, and blood chemistry profile parameters were examined to determine the safety of LDL-apheresis. There were a number of test results outside the normal ranges for blood components but these out-of-range values were either (1) present at the time of entry into the study, (2) transient or isolated, and/or (3) outside the normal range to such a minimal amount as to be considered not clinically significant. Most clinical laboratory results monitored during the study and follow-up period did not vary significantly from baseline levels. Fibrinogen, albumin, Immunoglobulin G (IgG) and total protein were lowered with LDL-apheresis treatment; however, the means were within the normal ranges in the defined patient population groups.

Decreases in hematocrit were noted in 3 patients. Two of these patients experienced active bleeding peptic ulcers identified before the treatment. The abnormalities for all three patients were slight and considered not clinically significant.

High blood sugars were noted in one patient before treatment with the LIPOSORBER® LA-15 System. This patient was known to have diabetes. Another patient had elevated alkaline phosphatase levels, presumably due to excessive Lovastatin therapy, which was resolved by decreasing the Lovastatin dosage.

5. Effect of Treatment on Baseline Lipid Levels

Baseline, i.e., pre-study, values of TC and LDL-C were compared with values of TC and LDL-C for the 3 patient groups after treatments had been stopped for a 4 week period. No statistically significant differences among the values were found for any patient group.

6. Updated Information

As of June 30, 1995, an additional 8 patients and 2 sites in the United States had been added to the study of the LIPOSORBER® LA-15 System, for a total of 72 patients at 11 sites. Forty seven of the 72 patients in the clinical trial were within the indicated patient population identified as Groups A, B or C. Thirty five of the 72 patients were treated for a minimum of 11 months. From December 14, 1988 through June 30, 1995, 4687 LDL-apheresis procedures had been performed. Based on statistical analysis of the additional information provided in this clinical update, the effectiveness of the device, measured by acute lowering of LDL-C and total cholesterol, did not change. However, the updated information did alter the safety information previously provided.

Updated information on adverse events is reported for the 72 patients enrolled in the study and an additional 2 patients, who did not fit the requirements for enrollment in the study but received treatments with the device under emergency use provisions. The following section on complications and adverse events includes the updated safety information.

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COMPLICATIONS AND ADVERSE EVENTS

Adverse reactions associated with the LIPOSORBER® LA-15 System are those anticipated for procedures involving extracorporeal circulation. During the course of 4,936 treatments in 74 patients* in the clinical study of the LIPOSORBER® LA-15 System, patients experienced the following adverse events as listed in Table 6:

Table 6

Summary of adverse events for all patients (74) during study and follow-up periods of the clinical trial

Reaction	Episodes		Patients	
Hypotension	41	0.8%	25	33.8%
Nausea/Vomiting	27	0.5%	14	18.9%
Flushing/Blotching	20	0.4%	9	12.2%
Angina/Chest pains	10	0.2%	8	10.8%
Fainting	9	0.2%	6	8.1%
Lightheadedness	7	0.1%	6	8.1%
Anemia	6	0.1%	6	8.1%
Abdominal discomfort	5	0.1%	3	4.1%
Numbness/Tingling	4	0.1%	4	5.4%
Tachycardia	4	0.1%	3	4.1%
Headache	3	0.1%	3	4.1%
Shortness of Breath	3	0.1%	2	2.7%
Hemolysis	3	0.1%	2	2.7%
Bradycardia	3	0.1%	2	2.7%
Itching/Hives	2	0.04%	2	2.7%
Blurred Vision	2	0.04%	2	1.4%

* Included in this patient total were: one patient with nephrotic syndrome (FGS) receiving emergency use treatments and one patient included in a special IDE supplement for an elevated Lp(a).

Single incidents of the following adverse events also occurred: arrhythmia, vasovagal reactions, prolonged bleeding, chills, diaphoresis and blood loss. In addition, one patient suffered blurred vision and a sensation of numbness in fingers and face when accidentally

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given a portion of an IV solution of the column regeneration fluid (5% saline) rather than the isotonic (0.9% saline) solution.

DEATHS

Six patients who had been enrolled in the clinical study between December 1988 through January 1996 died:

A 61 year old male, who had received 14 LDL-apheresis treatments ending on October 26, 1989, died in the Spring of 1990, from a malignant glioma of the brain.

A 44 year old male, who had received 91 LDL-apheresis treatments, died on September 30, 1992, from congestive heart failure resulting from pre-existing supravalvular aortic stenosis and coronary artery disease. This patient received his last treatment on September 4, 1991.

A 61 year old male, who had received 96 treatments and had multiple risk factors, including cerebrovascular disease with prior ischemic injury to brain, left ventricular mural thrombus, and hypertension, died on September 22, 1994, of cerebral hemorrhage. The patient received his last LDL treatment at 2 PM on September 20, 1994. That evening he suddenly complained of a headache about 10 PM and then became comatose. He did not regain consciousness before his death 2 days later. No autopsy was performed. It could not be determined if this incident was related to a coagulopathy due to therapy with the device.

A 50 year old male, who had smoked two packs of cigarettes per day for more than 30 years, died of lung cancer on April 22, 1990. This patient had received 5 LDL-apheresis treatments. This patient received his last treatment on October 2, 1989.

A 17 year old male died on May 14, 1995, from blunt trauma to the head suffered as a result of an accidental fall from a window. The patient had received 226 treatments over a period of 6 years.

A 72 year old male, died on January 13, 1996. The patient had received 150 treatments over 6.5 years. Treatments with the device were begun on August 7, 1989. On November 8, 1989, three months after starting therapy with the device, the patient suffered an MI and on January 3, 1990, the patient underwent a PTCA procedure. The patient received his last LDL treatment on January 9, 1996. Four days after this last treatment, the patient, who was at home, complained to his family of his usual anginal chest pain and laid down to rest. He was found dead in his bed a short time later. No autopsy was performed.

None of these deaths occurred during an LDL-apheresis procedure. Clinical investigators did not identify LDL-apheresis as a causal factor in any death. It cannot be concluded with

certainty however, due to the small size of the patient groups and the lack of a control group, whether any of the deaths were treatment related.

MYOCARDIAL INFARCTIONS

During the course of the clinical study, 3 MIs occurred. Only one of these 3 patients was still receiving treatments with the device when the cardiac event took place. No MI occurred during an actual LDL-apheresis procedure, and the clinical investigators did not identify LDL-apheresis as a causal factor in any case. The possibility that there is an increased risk of angina or MI in patients receiving this therapy cannot be totally excluded by the data derived from this study.

PATIENT ACCOUNTABILITY

Of the 34 patients in groups B and C of the original clinical trial, 15 discontinued treatment at some point during the clinical study. The most common reasons for stopping treatments were inconvenience of the procedure (4 patients) and financial burden (4 patients). None of the 5 patients in Group A discontinued their treatments.

X. CONCLUSIONS

The laboratory and clinical data provide reasonable assurance of the safety and effectiveness of the LIPOSORBER® LA-15 System when used as indicated in the labeling. A clinical study of the device supported the following conclusions:

1. Acute reductions in the range of 72-85% for LDL-C and 62-73% for TC were obtained for the three patient groups. LDL-C levels return to between 39 and 73 percent of baseline levels by day 7 and between 49 and 103 percent by day 14.

2. Acute lowering of HDL-C in conjunction with LDL-C may be anticipated. HDL-C was reduced the most (11-15%) in patients in Group A and the least (2-6%) in patients in Group C. Epidemiological studies have shown that both low HDL-C and high LDL-C are independent risk factors for coronary heart disease. The risk of acutely lowering HDL-C while lowering LDL-C is unknown.

3. The percent lowering of VLDL-C, Lp(a) and ApoB was comparable to the levels of lowering obtained for LDL-C.

4. Hematological, coagulation and blood chemistry profile parameters are not substantially affected by this treatment. Specifically, a slight lowering of fibrinogen may be anticipated although the mean levels remain with the normal range.

5. Adverse events which may be expected include, hypotension, nausea/vomiting, flushing/blotching, angina/chest pain, fainting, lightheadedness and anemia.

6. Therapy with the device has not been demonstrated to diminish the need for cardiovascular interventional procedures such as CABG, PTCA and endarterectomy.

7. The clinical studies using the LIPOSORBER® LA-15 System were not designed to address and did not establish any long-term clinical benefit of acute lowering of LDL-C.

XI. PANEL RECOMMENDATIONS

At an advisory meeting held on April 21, 1995, the Gastroenterology/Urology Devices Panel recommended that Kaneka America Corporation's PMA for the LIPOSORBER® LA-15 System be approved subject to submission of and approval by the Center for Devices and Radiological Health (CDRH) the following:

1. Labeling

   a. The device is to be indicated for the following patient populations:

      Group A. Functional Hypercholesterolemic Homozygotes with LDL-C > 500 mg/dl;

      Group B. Functional Hypercholesterolemic Heterozygotes with LDL-C ≥ 300 mg/dl; and

      Group C. Functional Hypercholesterolemic Heterozygotes with LDL-C ≥ 200 mg/dl and documented coronary heart disease.

      Any other population would need a randomized controlled clinical trial with angiographic evidence of a clinical benefit prior to approval.

   b. Only claims for acute lowering of LDL-C are to be included in the labeling. Claims of time-averaged or chronic lowering imply a clinical benefit that was not demonstrated in this trial.

2. Post-Approval Study

   All patients treated with this device will be enrolled in a registry and monitored.

3. Physician/Technical Personnel Training

   All physicians and technical persons providing therapy with the device will receive training prior to using the device.

4. Patient Brochure

   Patients will be fully informed of the risks and benefits of this therapy through a Patient Brochure.

Kaneka responded with revised labeling, details of an open-ended patient registry/post-approval study training, information on a physician/technician training program and a patient brochure. These additions meet the conditions of the Panel.

XII. CDRH DECISION

CDRH concurred with the recommendations of the Panel. Although there is a lack of data presented in the PMA to demonstrate the long-term benefits of lowering LDL-C using the LIPOSORBER® LA-15 System, there are numerous literature articles [1-9], which support the link between lowered LDL-C levels and a reduced risk of heart disease and coronary events. Patients in the three groups (A, B and C), described above, are considered to be at extreme risk for CHD due to their elevated LDL-C levels and their inability to reduce their LDL-C to recommended levels [5] using combined diet and drug therapies. Acute lowering of LDL-C by the LIPOSORBER® LA-15 System can be considered a clinical benefit for these 3 special patient populations. No other clinical benefit (e.g., reduction/prevention of coronary heart disease) due to lowering of LDL-C with the device has been demonstrated and therefore, no claims for any other benefit (e.g., reduction/prevention of CHD) can be made at this time.

Based on the data submitted and the clinical results, CDRH approved the PMA for the stated indications with the Patient Registry/Post-approval Study as specified in the approvable letter sent to the sponsor on October 13, 1995.

FDA inspection determined manufacturing facilities to be in compliance with the Good Manufacturing Practices Regulation.

CDRH approved this PMA on _____ .

XIII. APPROVAL SPECIFICATIONS

Directions for Use: See attached Labeling (Attachment A).

Patient Registry/Post-approval Study requirements and restrictions: The sponsor company has agreed to conduct an open-ended patient registry/post-approval study for every patient receiving treatments with the device following the approval order.

Expiration dating for the following components of device has been established and approved: 4 years for the SULFLUX® FS-05 Plasma Separator, 4 years for the LIPOSORBER® LA-15 Adsorption Column, and 3 years for the Plasmapheresis Tubing System (LT-MA2).

The sale, distribution, and use of this device are restricted to prescription use in accordance with 21 CFR 801.109 within the meaning of section 520(e) of the Federal Food, Drug, and Cosmetic Act (the act) under the authority of section 515(d)(1)(B)(ii) of the act. FDA has also determined that to ensure the safe and effective use of the device that the device is further restricted within the meaning of section 520(e) under the authority of section 515(d)(1)(B)(ii), (1) insofar as the labeling specify the requirements that apply to the training of practitioners who may use the device as approved in this order and (2) insofar as the sale, distribution, and use must not violate sections 502(q) and (r) of the act.

Warning, Hazards to Health from Use of the Device: See Indications, Contraindications, Warnings, Precautions and Adverse Reactions in the attached labeling.

XIV. REFERENCES

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FOREWORD

• About the LIPOSORBER® LA-15 System Operator's Manual

⚠ NOTICE

This manual is intended to be used with Software Version 1.0.

This Operator's Manual contains the information needed to operate the LIPOSORBER® LA-15 System correctly and safely. It is essential that you read this manual carefully and be sure you understand it before you operate the LIPOSORBER® LA-15 System. Pay particular attention to the Cautions and Warnings (Section 2) and to the items indicated by the safety alert symbol ⚠.

• Comments or Questions

All reasonable efforts have been made to assure the accuracy of the contents of the Operator's Manual. If you have any comments or questions regarding this manual or any questions that are not answered in this manual, contact Kaneka America Corporation.

Kaneka America Corporation
65 East 55th Street; 12th Floor
New York, NY 10022

Telephone: (800) KANEKAA (526-3522)
Fax: (212) 705-4350

• About the Safety Alert Symbol

The safety alert symbol ⚠ identifies situations that could be dangerous to the operator or the patient and directs your attention to the proper operation of the MA-01 Apheresis Machine. Read and understand each Warning, Caution and Notice thoroughly. See the next page of this manual for an explanation of these safety alerts.

LIPOSORBER® LA-15 SYSTEM

OPERATOR'S MANUAL

IMPORTANT

Before operating the MA-01 Apheresis Machine, review this Operator's Manual carefully and be sure you understand it. Pay particular attention to instructions marked with one of the following safety alert symbols.

This symbol calls attention to any condition or practice that, if not followed, can result in injury or death.

This symbol calls attention to any condition or practice that, if not followed, can result in patient and/or operator injury or damage to the MA-01.

This symbol calls attention to proper conditions and practices while operating the MA-01. Failure to follow these conditions and practices can result in patient and/or operator injury or damage to the MA-01.

Keep this Operator's Manual near the MA-01

• COMPONENTS

The LIPOSORBER® LA-15 System is an integrated, automated extracorporeal blood processing system that includes the following 3 disposables and a control/ monitor machine:

LIPOSORBER® LA-15 LDL Adsorption Column (disposable) comprised of two columns, each containing 150 ml of dextran sulfate cellulose adsorbent, and a membrane filter;

SULFLUX® FS-05 Plasma Separator (disposable) containing approximately 2800 polysulfone hollow fibers;

The Tubing System for Plasmapheresis (LT-MA2) (disposable); and

MA-01 Apheresis Machine, which monitors and controls the LDL-apheresis procedure.

[USE PATIENT GUIDE FIGURE]

Figure A. LIPOSORBER® LA-15 System overview.

• PRINCIPLES OF OPERATION

As illustrated in Figure A, the patient's blood is withdrawn via a venous access connected to the blood withdrawal line and enters the plasma separator. As blood flows through the hollow fibers in the plasma separator, plasma is separated and exits from the plasma separator outlet port. The remaining blood, including red and white blood cells and platelets, exits from the separator blood outlet port.

The cell-free plasma enters the plasma inlet port of one of the two LDL adsorption columns. As the plasma passes through the column, the apolipoprotein B-containing lipoproteins — LDL, VLDL, and Lp(a) — are selectively adsorbed in the column. There is minimal effect on HDL and other plasma components. The LDL-depleted plasma exits through the column plasma outlet and flows into the plasma return line of the extracorporeal circuit. After passing through the membrane filter, the LDL-depleted plasma is recombined with blood cells exiting the separator blood outlet port of the plasma separator and is returned to the patient via venous access.

When the first 500 ml of plasma has been treated with the left column, the MA-01 automatically switches the plasma flow to the right column. At this point, the plasma exiting the plasma separator flows into the right column, while the plasma remaining in the left column is flushed out by 140 ml of re-priming solution (Lactated Ringer's Injection, USP) and returned to the patient.

When recovery of the plasma from the left column is completed, the plasma return line is switched over from the left column to the right column, enabling the plasma in the right column to return to the patient. Throughout this column switch-over operation, the plasma pump and the regeneration pump are operated at the same speed. The re-priming solution during switch-over is not returned to the patient.

While the right column is treating plasma, the left column is rinsed with 105 ml of regeneration solution (5% Sodium Chloride Injection, USP), and its original adsorption capacity is restored. Along with the regeneration solution, apolipoprotein B-containing lipoproteins LDL, VLDL, and Lp(a) are flushed from the column through the waste line into the waste bag. When elution is completed, 355 ml of re-priming solution is pumped through the column to rinse out the regeneration solution completely and re-prime the column. The column is now ready for the next cycle of adsorption.

Subsequent switch-over and regeneration cycles are repeated every time 600 ml of plasma has been treated by one of the two LDL adsorption columns, allowing continuous LDL-apheresis until the predetermined plasma volume has been treated. The first switch-over occurs at 500 ml because initial levels of LDL, VLDL, and Lp(a) are higher in the first cycle.

Because the disposable components may not be reused, the MA-01 introduces air into the 2 LDL adsorption columns at the end of the return process. The tubing system, plasma separator, two LDL adsorption columns, and membrane filter are intended for single use only. All disposables must be discarded after each procedure.

Section 1. IMPORTANT INFORMATION FOR THE LIPOSORBER® LA-15 SYSTEM

TABLE OF CONTENTS

1.1. DESCRIPTION

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SULFLUX® FS-05 Plasma Separator (disposable) containing approximately 2800 polysulfone hollow fibers;

The Tubing System for Plasmapheresis (LT-MA2) (disposable); and

MA-01 Apheresis Machine, which monitors and controls the LDL-apheresis procedure.

Caution: **Federal law restricts this device to sale, distribution and use by or on the order of a licensed physician with appropriate training.**

This system may be used only as prescribed by a licensed and appropriately trained physician. While connected to the extracorporeal system, the patient must be attended at all times by a physician or qualified health-care professional adequately trained in all aspects of the procedure. All physicians and medical personnel utilizing the LIPOSORBER® LA-15 System **will be required** to have completed an appropriate training program. **Each patient treated with the system must be enrolled in a Patient Registry prior to the initiation of treatment.** Physicians using the device will be required, through the Patient Registry, to report periodically specified patient data regarding the treatments. Due to the continuing need to update information about therapy with the LIPOSORBER® LA-15 System, devices will only be sold to physicians who have agreed to participate in the follow-up Patient Registry. Physicians who do not comply with the Patient Registry reporting requirements will not be permitted to purchase additional disposable devices.

1.2. INDICATIONS FOR USE

The LIPOSORBER® LA-15 System is indicated for use in performing low density lipoprotein cholesterol (LDL-C) apheresis to acutely remove LDL-C from the plasma of the following high risk patient populations for whom diet has been ineffective and maximum drug therapy has either been ineffective or not tolerated:

Group A.	Functional Hypercholesterolemic Homozygotes with LDL-C > 500 mg/dl;
Group B.	Functional Hypercholesterolemic Heterozygotes with LDL-C ≥ 300 mg/dl; and
Group C.	Functional Hypercholesterolemic Heterozygotes with LDL-C ≥ 200 mg/dl and documented coronary heart disease.

The LDL-C levels for the indicated patient populations are baseline LDL-C levels obtained after the patient has had, at a minimum, a six-month trial of an American Heart Association (AHA) Step II diet (or equivalent) and maximum tolerated combination drug therapy designed to reduce LDL-C. Maximum tolerated combination drug therapy is an adequate trial of drugs from at least two separate classes of hypolipidemic agents such as, bile acid sequesterants, HMG-CoA reductase inhibitors, fibric acid derivatives, Niacin/Nicotinic Acid, etc. Documented coronary heart disease (CHD) includes documentation of coronary artery disease by coronary angiography or a history of myocardial infarction (MI), coronary artery bypass surgery (CABG), percutaneous transluminal coronary angioplasty (PTCA) or alternative revascularization procedure (e.g. atherectomy or stent), or progressive angina documented by exercise or non-exercise stress test. Baseline lipid levels are to be determined after stabilization on diet and drug therapy by making two measurements during a 2 to 4 week period. (Note: The two values should be within 10% of each other, indicating a stable condition.)

Although clinical benefit of LDL-C lowering has been documented in several diet, drug and/or surgical intervention trials, clinical studies using the LIPOSORBER® LA-15 System were not designed to address and did not establish the long-term clinical benefit of acutely lowering LDL-C.

1.3. CONTRAINDICATIONS

LDL apheresis with the LIPOSORBER® LA-15 System is contraindicated in patients:

(a) for whom the use of heparin would cause excessive or uncontrolled anti-coagulation or for whom adequate anticoagulation cannot be safely achieved, such as patients with hemophilia or patients who have had recent surgery; or

(b) with known hypersensitivity to heparin or ethylene oxide.

1.4. WARNINGS

1. The safety of LDL-apheresis treatment with the LIPOSORBER® LA-15 System occurring more than once a week or for treated volumes larger than two plasma volumes has not been determined.

2. **Patients who have received an ACE (angiotensin converting enzyme) inhibitor within the last 24 hours should not be treated. Therefore, the physician must monitor the use of ACE inhibitor medication on an ongoing basis with each treatment. Patients receiving an ACE inhibitor may experience an anaphylactoid-like reaction, including hypotension associated with flushing, dyspnea, and bradycardia. Such reactions, if left untreated, may be life-threatening.** The administration of ACE inhibitors also has been associated with the occurrence of tachycardia. **Risk of an anaphylactoid-like reaction or tachycardia may be minimized by the temporary cessation of the administration of ACE inhibitors for 24 hours or longer before each LDL-apheresis procedure depending upon whether the ACE inhibitor is a short- or long-acting dosage form.**

3. **LDL-apheresis treatment of patients who have taken any antihypertensive drugs within 24 hours of treatment may cause hypotension in such patients.** When clinically feasible, patients should not receive antihypertensive drugs during the 24 hour period prior to undergoing the LDL-apheresis procedure. Before each treatment, physicians should determine when patients took their last dose of such medication.

4. **Before using the LIPOSORBER® LA-15 System, carefully review the Operator's Manual. Persons performing the procedures must be qualified and have completed the required training program.** Users should follow all operating or maintenance procedures published by Kaneka America Corporation and use only those disposable device components recommended by Kaneka America. To do otherwise, may result in injury or loss of life.

5. Prior to initiating an LDL-apheresis procedure, carefully review the package inserts for all disposables and other materials to be used during the procedure. Failure to comply strictly with such package inserts, including the instructions for use, may result in serious injury to or possible death of patients.

6. Use special caution in patients where the extracorporeal volume of approximately 400 ml potentially will exceed 10% of the patient's blood volume. Such patients are at higher risk of experiencing hypovolemia, which is sometimes followed by hypotension.

7. Do not apply whole blood directly to the LIPOSORBER® LA-15 LDL Adsorption Column. This device is designed for perfusion of plasma only.

8. **Citrate preparation (ACD) <u>should never be used</u> as an anticoagulant in the system. The MA-01 Apheresis Machine is designed solely for treatment using heparin as an anticoagulant.** Anticoagulation is required to prevent thrombus formation from occurring within the extracorporeal circuit. Anticoagulation with too much heparin is associated with an increased risk of bleeding for the patient, especially after the procedure. In order to reduce the risk of bleeding, the puncture sites should be sufficiently compressed so that bleeding is stopped. (See Section 1.6.1(6) Notes for Potential Adverse Reactions.) **In some patients the potential for development of a coagulopathy extending several days post-therapy may exist.** In addition

to adjusting heparin dosage based on clinical observation during and after the apheresis procedure, Activated Clotting Time and/or partial thromboplastin time (PTT) values may be used. (See Section 1.8 Instructions for Use regarding "Determining Heparin Dosage.")

9. Make sure that the plasma flows in the direction of the arrow on the label of the LIPOSORBER® LA-15 Adsorption Column.

10. **Rinsing and subsequent priming of the fluid pathway of the disposables with appropriate solutions are necessary before commencing the procedure.** Because air bubbles in the disposables may lead to complications such as coagulation of plasma and impairment of performance, give full attention to measures that will prevent air-bubble migration into the disposables during rinsing and priming.

11. During an LDL-apheresis procedure, 0.9% Sodium Chloride Injection, USP, 5% Sodium Chloride Injection, USP, Lactated Ringer's Injection, USP, and Heparin Sodium Chloride Injection, USP, are used. Carefully identify each solution and ensure that it is properly connected to the LIPOSORBER® LA-15 System. **Using the incorrect solution may result in serious injury or possible death.**

12. While operating, the differential pressure across the LIPOSORBER® LA-15 Adsorption Column must be **under 100 mmHg, and the transmembrane pressure (TMP) of the SULFLUX® FS-05 Plasma Separator must be under 50 mmHg.** If either an extreme pressure drop across the column or an extreme TMP occurs, the blood flow rate and/or plasma separation rate should be lowered appropriately or even stopped if necessary.

13. **To minimize the risk of air embolism, the return tubing line must be connected to the air bubble detector.**

14. In case of a power failure or system shutdown, terminate the procedure immediately according to the instructions provided in the Operator's Manual for the LIPOSORBER® LA-15 System.

15. No chemicals or solvents are to be used either inside or outside of the disposables.

1.5. PRECAUTIONS

1. The long-term safety and efficacy of LDL-apheresis using the LIPOSORBER® LA-15 System have not been established. (See Section 1.7 Clinical Experience.)

2. The safety and efficacy of LDL-apheresis using the LIPOSORBER® LA-15 System has not been established for pregnant women or for women during the lactation period, e.g. the effect of treatments on folic acid levels has not been determined.

3. The safety and efficacy of LDL-apheresis using the LIPOSORBER® LA-15 System have not been established for: (1) patients less than 15 kg in body weight; (2) patients less than 5 years of age; (3) patients with certain cardiac impairments such as uncontrolled arrhythmia, unstable angina, decompensated congestive heart failure or valvular disease; and (4) patients with renal or thyroid disease or liver abnormalities.

4. LDL-apheresis should be considered a lifetime therapy since, upon discontinuation of therapy, lipid levels will return to pre-treatment levels or higher. Diet and drug therapy must be maintained during the treatment period as the rate of rebound will accelerate if lipid-lowering drug therapy is discontinued.

5. The SULFLUX® FS-05 Plasma Separator, LIPOSORBER® LA-15 Adsorption Column, and the Tubing System for Plasmapheresis (LT-MA2) are disposable and are **intended for use in a single procedure only. Never reuse.** Discard the disposables after each procedure.

6. Physicians and operators should follow the OSHA and the CDC/ACIP Adult Immunization Guidelines for Hemodialysis Patients. It is recommended that patients be screened for Hepatitis B and other infectious diseases; however, due to possible exposure to hepatitis virus, human immunodeficiency virus, and other infectious agents when handling extracorporeal blood circuits, blood or blood products, universal precautions should be taken at all times to prevent the exposure to and transmission of such agents.

7. When disposing of the disposable device components and wastes, comply with all local requirements and the policy of the facility regarding precautions for and prevention of infection and environmental pollution.

8. Medical personnel should monitor the patient for adverse symptoms at all times during treatment and should be trained as to the protocol for responding with appropriate interventions. (See Section 1.6.1 Notes for Potential Adverse Reactions)

9. Closely monitor patient clotting time periodically during the procedure to ensure that an adequate level of anticoagulation is maintained.

10. Patient's cholesterol levels (TC, LDL-C, HDL-C, etc.) should be monitored every 3 months during the course of long-term therapy. Samples for cholesterol levels should be taken immediately before and after a given LDL-apheresis procedure.

11. High density lipoprotein cholesterol (HDL-C) may be acutely reduced by up to 14% post-treatment. Epidemiologic studies have shown that both low HDL-C and high LDL-C are independent risk factors for coronary heart disease. The risk of acutely lowering HDL-C while lowering LDL-C with this device is unknown.

12. Instructions for heparin administration should be followed as stated in the guidance provided by the manufacturer in the Operator's Manual for the LIPOSORBER® LA-15 System. The amounts of heparin outlined in the Operator's Manual are intended as general suggestions. **The exact amount, frequency and method of administration of heparin are the sole responsibility of the prescribing/attending physician and should be selected based on the individual patient's clinical condition.**

13. All connections of the extracorporeal circuit should be checked carefully prior to initiating and during the procedure. Avoid unnecessary kinking of the tubing lines and the patient's vascular access devices at all times.

14. Drip chambers in the extracorporeal circuit should be kept at least 2/3 to 3/4 full and monitored at all times in order to decrease the risk of air embolism.

15. The fluid circuit of this system is intended to be sterile and nonpyrogenic. Aseptic handling techniques are necessary to maintain these conditions. Check the packaging for the disposable device components to ensure that it is intact. Do not use a disposable product if the package, sterile bag, protective cap or the product itself is damaged. Do not open the sterile bags containing the disposables until use.

16. The LIPOSORBER® LA-15 System includes a blood warmer with a temperature setting range of 35-40°C. It is recommended that the blood warmer be set at a temperature between 36-38°C in order to avoid significant decreases in blood temperature during extracorporeal circulation.

17. In transporting and storing the device components, handle with care and store all disposables in a clean and secure area at room temperature (5-30°C), avoiding exposure to direct sunlight, high humidity or excessive vibration. **Handle the SULFLUX® FS-05 Plasma Separator and the LIPOSORBER® LA-15 Adsorption Column with care to avoid dropping or other sudden impacts and never allow them to freeze. Do not use components which may have been damaged or frozen.**

1.6. ADVERSE EVENTS

During the course of the clinical study from December 1988 through June 1995, 74 patients[1] had received 4,936 treatments using the LIPOSORBER® LA-15 System. Prior to enrollment in the clinical study, 76% of the patients had documented coronary heart disease, and 26% of all patients previously had a myocardial infarction. Upon enrollment in the clinical study, 74% of the patients had LDL-cholesterol levels exceeding 200 mg/dl after diet and maximum drug therapy. Patients who were receiving or had received LDL-apheresis therapy with the LIPOSORBER® LA-15 System experienced the following adverse events:

Adverse Events Experienced During LDL-Apheresis Procedures

Patients in the clinical study experienced the following adverse events during LDL-apheresis procedures using the LIPOSORBER® LA-15 System:

Table 1.1.

Adverse Event	Episodes		Patients	
Hypotension	41	0.8%	25	33.8%
Nausea/Vomiting	27	0.5%	14	18.9%
Flushing/Blotching	20	0.4%	9	12.2%
Angina/Chest pains	10	0.2%	8	10.8%
Fainting	9	0.2%	6	8.1%
Lightheadedness	7	0.1%	6	8.1%
Anemia	6	0.1%	6	8.1%
Abdominal discomfort	5	0.1%	3	4.1%
Numbness/Tingling	4	0.1%	4	5.4%
Tachycardia	4	0.1%	3	4.1%
Headache	3	0.1%	3	4.1%
Shortness of Breath	3	0.1%	2	2.7%
Hemolysis	3	0.1%	2	2.7%
Bradycardia	3	0.1%	2	2.7%
Itching/Hives	2	0.04%	2	2.7%
Blurred Vision	2	0.04%	2	1.4%

[1] Included in this patient total are one emergency use patient treated for nephrotic syndrome (FGS) and one patient with coronary heart disease treated under a special IDE supplement for an elevated Lp(a) level.

Single incidents of the following adverse events also occurred: Arrhythmia; vasovagal reaction; bleeding (prolonged); chills; diaphoresis; and blood loss.

Deaths

Six patients who had been enrolled in the clinical study between December 1988 through January 1996 died:

Forty-four year old male died on September 30, 1992 from congestive heart failure resulting from preexisting supravalvular aortic stenosis and coronary artery disease. Patient had ceased receiving LDL-apheresis treatment more than a year earlier.

Seventeen year old male, who had received 226 treatments, died on May 14, 1995 from blunt trauma to the head suffered as a result of an accidental fall from a window after consuming alcohol.

Seventy-two year old male, who had received 150 LDL-apheresis treatments, died on January 13, 1996, apparently from a heart attack resulting from severe, preexisting coronary heart disease, including two prior myocardial infarctions, a stroke, and two coronary artery bypasses.

Sixty-one year old male, who had received 14 LDL-apheresis treatments, died in the spring of 1990, from a malignant glioma of the brain.

Sixty-one year old male who had received 96 treatments and had multiple risk factors, including cerebrovascular disease with prior ischemic injury to brain, left ventricular mural thrombus, and hypertension, died on September 22, 1994 of cerebral hemorrhage.

Fifty year old male, who had smoked two packs of cigarettes per day for more than 30 years, died on April 22, 1990 of lung cancer with metastases to the liver.

None of these deaths occurred during an LDL-apheresis treatment, and the clinical investigators for the patients did not identify LDL-apheresis as a causal factor. However, it cannot be concluded with certainty, due to the small size of the patient groups and the lack of a control group, whether any of the deaths were treatment related.

Myocardial Infarctions

During the course of the clinical study, three MIs occurred: Two occurred in patients who were no longer receiving treatment. No MI occurred during an actual LDL-apheresis procedure, and the clinical investigators for the patients did not identify LDL-apheresis as a causal factor. The possibility that there is an increased risk of angina or MI in patients receiving this therapy cannot be totally excluded.

Other Potential Adverse Events

Although patients participating in the clinical study did not experience the following adverse events during the reported 4,936 treatments, such events may occur in procedures involving extracorporeal circulation: uncontrolled bleeding; infectious disease transmission, including hepatitis; sepsis due to circuit contamination; air embolism, and hypersensitivity reactions.

Other complications may include: plasma loss from circuit leaks; coagulopathy potentially extending several days post treatment; and volume shifts. Equipment malfunction or user error may result in fluid volume abnormalities which may require acute medical intervention.

Patients on antihypertensive drugs, such as diuretics, calcium antagonists, beta blockers and ACE inhibitors, are at increased risk of hypotensive reactions occurring during therapy. ACE inhibitors have been associated with severe hypotension associated with flushing, dyspnea, and bradycardia. Therefore, **ACE inhibitors should not be administered for 24 hours or longer preceding each apheresis procedure. (See Warnings.) In order to minimize the potential risks which also may be associated with other anti-hypertensive medications, it is recommended that patients refrain from taking antihypertensive drugs** at least the day before the LDL-apheresis procedure, when clinically feasible. Before each treatment, patients should be requested to advise the attending physician when they last took a dose of such medication. One of the hypotensive events reported in Table 1.1 was attributed to the administration of ACE inhibitors. The administration of ACE inhibitors in conjunction with therapy with the device also has been associated with the occurrence of tachycardia, and three of the reported tachycardia events (two in an emergency use patient) were attributed to the administration of ACE inhibitors.

Reduction in Serum Components

LDL-apheresis is known to decrease the selected serum components listed below. The long-term effects of such reduction have not been established.

Table 1.2.

Serum Component	Acute Percentage Reduction (%)
Hemoglobin	1.4
Vitamin E (α-tocopherol)*	63
Vitamin E (γ-tocopherol)*	55
Albumin	14
Fibrinogen	29
Platelets	17

* *Data for the acute reductions in these serum components also included limited data from follow-up treatments.*

1.6.1. Notes for Potential Adverse Events

If a patient experiences an adverse reaction during a procedure, the physician should stop the procedure until the cause of the reaction has been determined and the patient's condition stabilized. The physician should determine all medical responses to adverse reactions based upon the individual patient's physical condition. However, certain reactions that may be anticipated are identified below with common medical treatment responses.

(1) Hypotension. The procedure should be stopped, and the patient should be placed in the Trendelenburg position and/or receive a fluid challenge. If the hypotension persists, the procedure should be terminated.

Note: For an "anaphylactoid" like reaction, administration of epinephrine, sympathomimetic drugs, prednisolone, anti-histamines, and/or calcium have been reported by clinicians as effective interventions.

(2) Nausea and Vomiting. The procedure should be stopped and the etiology of the nausea and vomiting investigated (e.g. hypotension).

(3) Flushing/Blotching. Check vital signs and reduce the blood flow rate. If symptoms are persistent or repetitive, consider the administration of Benadryl.

(4) Angina/Chest Pain. The procedure should be stopped and medical therapy instituted at the discretion of the physician. If the angina persists, the procedure should be terminated.

(5) Fainting/Lightheadedness. See hypotension.

(6) Anemia. May be minimized by the appropriate use of iron supplements. Clinical symptoms may appear when hemoglobin is below 11 g/dl in men and 10 g/dl in women.

(7) Prolonged Bleeding (at cannulation site after removing venous cannulae). Direct manual pressure should be applied until the bleeding stops. If prolonged bleeding occurs (in excess of 20 minutes), adjustment of the heparin dosing may be necessary. It is recommended that, during the subsequent procedure, the heparin dose be reduced and monitored by Activated Clotting Time (ACT). **Repetitive LDL apheresis treatment may affect the patient's clotting time.** Therefore, a periodic check, e.g. every 3 months, of other relevant coagulation parameters is recommended, including the number of thrombocytes and the fibrinogen concentration, in order to ensure that these parameters are sufficient to maintain adequate coagulation.

(8) Hemolysis as Evidenced by Discoloration of Plasma or Hemolysis as Indicated by Activation of the Blood Leak Detector Alarm of the MA-01 Apheresis Machine. If either indicator of hemolysis occurs, the procedure should be terminated and the patient's hematocrit, urine output and kidney function monitored.

1.7. CLINICAL EXPERIENCE

The clinical study of the LIPOSORBER® LA-15 System was conducted at 11 clinical sites in the United States with 72 patients (of whom 47 patients were within the indicated patient population identified in Section 1.2 and 35 were treated for a minimum of 11 months), and data were reported for 4,687 LDL-apheresis procedures performed from December 14, 1988 through June 30, 1995. The clinical patient population did not include pregnant women; patients less than 15kg in body weight; patients less than 5 years of age; and patients with end stage renal disease, thyroid disease or liver abnormalities. Under the clinical protocol, a 6-week period of baseline stabilization was followed by a 22-week study period consisting of 18 weeks of treatments, which were divided into 3 courses of 6 weeks each, and a 4-week rebound study during which the change in lipid levels on diet and drug therapy were observed. During the study period, patients were maintained on diet and maximum tolerated lipid-lowering drug therapy and treated with the LIPOSORBER® LA-15 System, typically once every week for Group A and Group B patients and once every 2 weeks for Group C patients. Thereafter, patients were offered the opportunity to continue to receive LDL-apheresis therapy.

Detailed effectiveness data were reported and statistically analyzed from 2,229 LDL-apheresis procedures performed from December 14, 1988 through September 30, 1991 in 64 patients (of whom 39 patients were within the indicated patient population identified in Section 1.2 and 29 were treated for a minimum of 11 months). The clinical study of these patients demonstrated that treatment with the LIPOSORBER® LA-15 System resulted in an acute lowering of LDL-C of approximately 75% to 80%. However, the LDL-C levels rebounded at a nonlinear rate (more rapidly immediately post-treatment) as shown. (Table 1.4)

Adverse events data were reported for 74 patients[2] and 4,936 treatments performed from December 14, 1988 through June 30, 1995. The adverse events experienced by these 74 patients during LDL-apheresis procedures with the LIPOSORBER® LA-15 System are summarized in Table 1.1 above. All deaths and myocardial infarctions experienced by patients who were treated with the LIPOSORBER® LA-15 System during that time period also are reported in Section 1.6 Adverse Events.

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[2] Included in this patient total are one emergency use patient treated for nephrotic syndrome (FGS) and one patient with coronary heart disease treated under a special IDE supplement for an elevated Lp(a).

1.8. INSTRUCTIONS FOR USE

The LIPOSORBER® LA-15 System is indicated for use in performing low density lipoprotein cholesterol (LDL-C) apheresis to acutely remove LDL-C from the plasma of the following high risk patient populations for whom diet has been ineffective and maximum drug therapy has either been ineffective or not tolerated:

Group A.	Functional Hypercholesterolemic Homozygotes with LDL-C > 500 mg/dl;
Group B.	Functional Hypercholesterolemic Heterozygotes with LDL-C ≥ 300 mg/dl; and
Group C.	Functional Hypercholesterolemic Heterozygotes with LDL-C ≥ 200 mg/dl and documented coronary heart disease.

The LDL-C levels for the indicated patient populations are baseline LDL-C levels obtained after the patient has had, at a minimum, a six-month trial of an American Heart Association (AHA) Step II diet (or equivalent) and maximum tolerated combination drug therapy designed to reduce LDL-C. Maximum tolerated combination drug therapy is an adequate trial of drugs from at least two separate classes of hypolipidemic agents such as, bile acid sequesterants, HMG-CoA reductase inhibitors, fibric acid derivatives, Niacin/Nicotinic Acid, etc. Documented coronary heart disease includes documentation of coronary artery disease by coronary angiography or a history of myocardial infarction (MI), coronary artery bypass surgery (CABG), coronary angioplasty or alternative revascularization procedure (e.g. atherectomy or stent), or progressive angina documented by exercise or non-exercise stress test.

Effectiveness of the therapy will be influenced by the treatment frequency and the amount of plasma treated.

Determining Treatment Frequency:

Prior to initiation of therapy, baseline lipid levels should be determined after stabilization on maximum diet and drug therapy by taking two measurements during a two to four week period. (Note: The two values should be within 10% of each other to be acceptable.)

Treatment with LDL-apheresis provides an immediate acute reduction in a patient's lipid levels compared to pre-treatment lipid levels. The acute effects of an LDL-apheresis treatment on serum lipids and lipoproteins may be summarized as follows:

Table 1.3. Acute Percentage Reductions In Lipids And Lipoproteins Achieved During The Study Period Of The Clinical Trial Of The LIPOSORBER® LA-15 System.

Lipid/Lipoprotein	Acute Percentage Reduction (%)
Total cholesterol	61 - 71
LDL-C	73 - 83
HDL-C	3 - 14
Lp(a)	53 - 76
Triglycerides	47 - 68

Therapy with the LIPOSORBER® LA-15 System does not produce a sustained lowering of lipid levels. A patient's LDL-C level will increase (or rebound) immediately after treatment at a nonlinear rate (more rapidly immediately post-treatment) as shown in the following table:

Table 1.4. Rebound Of LDL-C After Treatment During Study Period.

	Cumulative Mean Percentage Rebound to Baseline (%)		
No. of Days After Treatment	Group A (N*=5)	Group B (N=10)	Group C (N=22)**
1	9 - 19	8 - 18	6 - 16
2	14 - 26	15 - 25	20 - 32
3	23 - 39	25 - 35	24 - 56
5	31 - 51	38 - 52	42 - 58
7	39 - 57	43 - 73	47 - 73
14	49 - 91	69 - 99	65 - 103

* *N = number of patients*

** *Group C also included two control patients who were not included in this analysis of study patients.*

With regular apheresis treatments, a patient's LDL-C level can be maintained below the baseline level. Without regular treatment, a patient's LDL-C level will rebound to the baseline level or higher. In addition, the rate of rebound shown above will accelerate if diet and lipid-lowering drug therapy is discontinued, therefore, a **patient's diet and drug therapy must be maintained.**

Because of the heterogenous nature of Hypercholesterolemia, dosing and response to therapy vary among patients, resulting in the need for individualized treatment prescriptions. It is recommended that, shortly after the initiation of therapy, the physician measure a rebound curve for each patient to aid in determining the appropriate treatment interval. Rebound curves are determined by measuring the patient's lipid level immediately following treatment and at several intermediate points before the next treatment. If the patient changes or discontinues lipid-lowering medication while undergoing LDL-apheresis, the rebound curve should be reestablished.

The original clinical trial of 64 patients (29 indicated patients with greater than 11 months of therapy) using the LIPOSORBER® LA-15 System has suggested that **patients in Groups A and B of the indicated population should be treated at a frequency of once every week, while patients in Group C should be treated once every two weeks as part of a life-long maintenance therapy.**

Determining Plasma Volume to be Treated:

The clinical study has established that treating 1.5 patient plasma volumes during a single procedure will yield a 75% to 80% acute reduction in LDL-C. The plasma volume to be treated can be calculated as follows:

1. Obtain the following patient information:

   Sex (male or female)
   Height (centimeters)
   Weight (kilograms)
   Hematocrit (%)

2. Refer to the appropriate table below (male or female) and, using the patient's height and weight, locate the factor (number) at their intersection.

MALE

Table 1.5. Factor To Calculate Plasma Volume To Be Treated.

Weight (kg) \ Height (cm)	100	110	120	130	140	150	160	170	180	190	200	210
140	82	84	86	89	92	95	99	104	109	114	121	128
135	80	82	84	86	89	93	97	101	106	112	118	125
130	77	79	81	84	87	90	94	99	104	110	116	123
125	75	77	79	82	85	88	92	96	102	107	113	120
120	73	74	77	79	82	86	90	94	99	105	111	118
115	70	72	74	77	80	83	87	92	97	102	109	116
110	68	70	72	74	77	81	85	89	94	100	106	113
105	65	67	69	72	75	78	82	87	92	98	104	111
100	63	65	67	69	72	76	80	84	89	95	101	108
95	60	62	64	67	70	74	77	82	87	93	99	106
90	58	60	62	65	68	71	75	80	85	90	97	103
85	56	57	60	62	65	69	73	77	82	88	94	101
80	53	55	57	60	63	66	70	75	80	85	92	99
75	51	53	55	57	60	64	68	72	77	83	89	96
70	48	50	52	55	58	61	65	70	75	81	87	94
65	46	48	50	53	56	59	63	67	73	78	84	91
60	44	45	48	50	53	57	61	65	70	76	82	89
55	41	43	45	48	51	54	58	63	68	73	80	87
50	39	41	43	45	48	52	56	60	65	71	77	84
45	36	38	40	43	46	49	53	58	63	69	75	82
40	34	36	38	40	43	47	51	55	60	66	72	79
35	31	33	35	38	41	45	49	53	58	64	70	77
30	29	31	33	36	39	42	46	51	56	61	68	75
25	27	28	31	33	36	40	44	48	53	59	65	72
20	24	26	28	31	34	37	41	46	51	56	63	70
15	22	24	26	28	31	35	39	43	48	54	60	67

FEMALE

Table 1.6. Factor To Calculate Plasma Volume To Be Treated.

Weight (kg) \ Height (cm)	100	110	120	130	140	150	160	170	180	190	200	210
140	78	79	81	84	87	90	94	98	103	109	115	122
135	75	77	79	81	84	88	92	96	101	106	112	119
130	73	74	76	79	82	85	89	93	98	104	110	117
125	70	72	74	77	79	83	87	91	96	101	108	114
120	68	69	72	74	77	80	84	89	93	99	105	112
115	65	67	69	72	74	78	82	86	91	96	103	109
110	63	64	67	69	72	75	79	84	88	94	100	107
105	60	62	64	67	70	73	77	81	86	91	98	104
100	58	59	62	64	67	70	74	79	84	89	95	102
95	55	57	59	62	65	68	72	76	81	87	93	99
90	53	55	57	59	62	65	69	74	79	84	90	97
85	50	52	54	57	60	63	67	71	76	82	88	94
80	48	50	52	54	57	60	64	69	74	79	85	92
75	45	47	49	52	55	58	62	66	71	77	83	89
70	43	45	47	49	52	56	59	64	69	74	80	87
65	40	42	44	47	50	53	57	61	66	72	78	84
60	38	40	42	44	47	51	54	59	64	69	75	82
55	35	37	39	42	45	48	52	56	61	67	73	80
50	33	35	37	39	42	46	49	54	59	64	70	77
45	30	32	34	37	40	43	47	51	56	62	68	75
40	28	30	32	34	37	41	44	49	54	59	65	72
35	25	27	29	32	35	38	42	46	51	57	63	70
30	23	25	27	29	32	36	40	44	49	54	60	67
25	20	22	24	27	30	33	37	41	46	52	58	65
20	18	20	22	24	27	31	35	39	44	49	55	62
15	16	17	19	22	25	28	32	36	41	47	53	60

3. Multiply the factor determined in Step 2 by (100 - hematocrit).

4. Round up value from Step 3 to the nearest hundredth. This is the plasma volume to be treated.

Example:

STEP 1: Obtain patient information.

Sex:	Male
Height:	177 cm
Weight:	73 kg
Hematocrit:	38%

STEP 2: Use Table 1.5 (Male). Using the patient's height and weight, locate the factor at their intersection. Use next highest height (180 cm) and weight (75 kg). Factor → **77**

STEP 3: Multiply value from STEP 2 by (100 - hematocrit) → **77 x (100 - 38) = 4,774**

STEP 4: Round up value from STEP 3 to the nearest hundredth → **4,800 ml**
This is the plasma volume to be treated.

The amount of plasma treated and the frequency of treatment will require adjustment as clinically indicated by the physician in order to achieve and optimize individualized patient treatment goals. The patient should be maintained on diet and maximum tolerated lipid-lowering drug therapy. The patient should be clearly informed that if this therapy is to achieve continued acute lowering of LDL-C levels, it must be performed as part of a life-long treatment..

The safety of LDL-apheresis treatments performed more often than once a week or on volumes larger than two plasma volumes has not been determined.

Determining Heparin Dosage:

Although heparin administration procedures vary and are adjusted to the requirements of the individual patient by a supervising physician, a proper heparinization schedule **must** be initiated before and maintained throughout LDL-apheresis to prevent clotting and subsequent blood path obstruction. The following are examples of heparinization schedules.

1. Priming Solution. Lactated Ringer's Injection, USP (1,000 ml) should contain 2,000-3,000 USP units of heparin.

2. Loading Dose (Manual Infusion). Obtain PTT and PT pretreatment levels prior to initiation of LDL-apheresis therapy. If values are in the normal range, the recommended loading dose is approximately 25 USP units of heparin per kilogram of body weight. If a patient's PTT or PT is abnormally high, the physician should consider a lower loading dose of heparin.

3. Continuous Heparinization. Continuous heparinization is required during the LDL-apheresis procedure. Based upon a normal PTT and PT, approximately 25 USP units of heparin per kilogram of body weight per hour is recommended. During the first few apheresis treatments, coagulation test results should be monitored frequently to establish a coagulation profile for the individual patient. A monitoring schedule for these initial treatments should consist of a pre-heparinization PTT, PT, and activated clotting time (ACT) measurement. The ACT measurements should be performed at 30-minute intervals during the treatment. ACT levels should be maintained within a range of 150-300 seconds or 1.5 to 3 times the normal range. Once a patient's heparin regimen has been established, a patient's ACT may be followed less frequently during subsequent treatments.

A heparin pump is used to deliver heparin into the blood withdrawal line at a rate necessary to maintain a desired clotting time. A heparin pump infusion rate between 1,000-3,000 USP units of heparin per hour usually is sufficient.

For an adult weighing 60 to 80 kg, a typical loading dose would be 1,500 to 2,000 USP units followed by a recommended continuous heparin rate of 1,500 to 2,000 USP units per hour.

Detailed Instructions for Use are set forth in the accompanying Operator's Manual for the LIPOSORBER® LA-15 System and in the package inserts for the LIPOSORBER® LA-15 Adsorption Column, SULFLUX® FS-05 Plasma Separator, and Tubing System for Plasmapheresis (LT-MA2). **The procedures outlined in the Operator's Manual must be followed exactly as specified. No adjustments or modifications of such procedures not specifically stated in the Operator's Manual may be made. In the event of equipment or device failure or malfunction, discontinue the procedure and follow the instructions in the Operator's Manual.**

1.9. LIMITS TO THE MANUFACTURER'S RESPONSIBILITY

- The LIPOSORBER® LA-15 System must be used in accordance with this Operator's Manual. **The use of operating or maintenance procedures other than those published by Kaneka America Corporation or the use of disposable device components not recommended by Kaneka America may result in injury or loss of life.** Kaneka America, the manufacturers of the MA-01 or the disposable device components, or any distributor of the LIPOSORBER® LA-15 System will not be responsible for resulting injury or damage if the procedures to operate and maintain the LIPOSORBER® LA-15 System are other than those specified by Kaneka America in the Operator's Manual. Persons performing the procedures must be appropriately trained and qualified.

- In no event shall Kaneka America or the manufacturers of the MA-01 or of the disposable device components or any distributor of the LIPOSORBER® LA-15 System be liable for any losses or damages caused or resulting from any negligence in the selection of patients outside the indicated population, operation of the LIPOSORBER® LA-15 System, or treatment of patients with the LIPOSORBER® LA-15 System by any third party.

- Except as expressly set forth herein, Kaneka America makes no warranty whatsoever, express or implied, and **specifically disclaims any warranty of merchantability or fitness for a particular purpose** as to the LIPOSORBER® LA-15 System.

- **In no event shall Kaneka America, the manufacturers of the MA-01 or of the disposable device components or any distributor of the LIPOSORBER® LA-15 System be liable for any special, consequential or incidental losses or damages for any reason.**

- Certain solutions and disposable products available from other manufacturers are used with the LIPOSORBER® LA-15 System. Kaneka America has no control over variability, tolerances, mechanical strength or changes in these products which may exist from time to time. Therefore, Kaneka America cannot ensure that the disposable products of other manufacturers will function in a satisfactory manner and expressly disclaims any responsibility or liability for any injury, harm, damages or loss resulting from the use or malfunction of such products.